INTRODUCTION

Erythema multiforme (EM) is an acute heterogeneous immune-mediated disease, that clinically presents with a distinctive skin eruption on extremities and trunk, with or without mucous membrane affection [1, 2]. It is a relatively infrequent disease, representing between 0.1-1% of all dermatologic outpatients in the U.S. or 1 to 6 cases per million population per year [2]. EM can be induced or triggered by various factors as medications or infections, in particular herpes simplex virus (HSV) infection [3]. Herpes simplex associated erythema multiforme (HAEM) presents with skin and mucosal affection, acute or recurrence, sometimes self-limited course and is caused by the HSV induced T-cell mediated immune response [4]. We present a case report of herpes associated erythema multiforme in a female patient with recurrent labial HS.

CASE REPORT

A 44-year-old woman was consulted with complaints of recurrent herpes of the upper lip from one year.
After the last herpes episode, rounded target-like lesions appeared on the dorsal surface of both hands. The patient was in unaffected general condition and afebrile. She denied any concomitant deceases and prescribed medication except for panic disorder symptoms associated with previous herpes simplex episodes as well as local acyclovir creme.

Dermatological examination revealed typical target plaques with erythematous elevated periphery and centered vesicle or hemorrhagic crust on the dorsal surface of both hands (Fig. 1). No mucous membranes lesions and no pathological findings in the somatic status were found. The routine laboratory investigations were within normal ranges and the serology for lues was negative. However, the patient had elevated titer of anti HSV-1 IgG antibodies in sera.

The histological examination from skin lesions showed necrotic epidermis with the presence of apoptotic keratinocytes, edema in the papillary dermis and perivascular inflammatory infiltrate, confirming the diagnosis EM (Fig. 2).

Therapy with acyclovir 5 x 200 mg/24 h, dexamethasone 4 mg/24 h and topical therapy with clobetasol propionate was initiated, however due to increased anxiety and tachycardia reported by the patient the corticosteroid therapy was discontinued. Promethazine recommended by a psychiatrist was added and the patient had a significant improvement during the follow-up visit on the tenth day.

**DISCUSSION**

The first description of erythema (exudativum) multiforme was performed in 1866 by Ferdinand von Hebra [5]. Since then, it is still disputable if EM is a separate mild disease [6], or is a group of at least 3 clinical variants with different severity: EM (minor or major), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and SJS/TEN overlap [7-9]. Clinical presentation of EM consists of typical target-like or “iris-like” plaques with rounded slightly elevated periphery, centered by erythematous macule, vesicle or bulla, and are distributed on the extremities and rarely on trunk [6]. In opposite, in severe diseases like SJS, and TEN, target lesions on skin are rare, predominate bullas and broad erosions, and mucosal and internal organ affection is frequent [6, 8]. Hence some argue that EM is almost always infection triggered disease, while SJS and TEN are exclusively drug induced conditions, almost never recurred and are part of Severe Cutaneous Adverse Reactions (SCAR) [9, 10].

Many studies highlight that the pathogenesis of HAEM corresponds to a delayed hypersensitivity reaction [4, 10-12]. Manifestations of the disease begin with the transport of HSV DNA by circulating mononuclear CD34+ cells to keratinocytes [1, 10]. They ingest the virus and fragment DNA, leading to the appearance of HSV-specific CD4 + Th1 cells and contributing to the inflammatory response [10, 12]. CD4+ cells release interferon-γ (IFN-γ), which initiates an inflammatory cascade in response to viral antigens and initiates immunomodulated epidermal damage [10, 13]. Both HSV 1 and HSV 2 can trigger the EM lesions. PCR has been employed to detect the presence of HSV DNA in HAEM lesions and tissues [14]. HSV genes can also be identified with reverse transcriptase PCR or immunohistochemistry using antibodies to specific viral genes [15]. Finally, it is suggested that HAEM needs certain genetic background. Mainly patients who are HLA A33, B15, B35,
DR53, DQB1*0301 and DQw3 alleles carriers can develop HAEM, while others may have only HS lesions [16].

The therapy of erythema multiforme depends on the suspected trigger and the disease severity. If the EM is severe, effective treatment is with prednisolone up to 0.5 mg/kg/24 h in tapered doses for suppressing the disease. However, systemic corticosteroids are regarded controversial, since it could facilitate persistence of the triggering infection and should be limited to 15 days [12]. Antiviral therapy (acyclovir or valacyclovir) is usually ineffective if initiated when lesions occur, but is highly efficient for prophylaxis [17]. Single successful results for therapy with cyclosporin, cyclophosphamide, levamisole, thalidomide, dapsone, apremilast and adalimumab have also been reported [18]. Local wound care, topical corticosteroid cream or lotions, topical, analgesics or anesthetics for pain control are also important [1, 12].

In conclusion erythema multiforme is an acute, immune-mediated disease commonly caused by HS infection and certain medications. The diagnosis of HAEM is easily made when the patient develops typical target lesions and previous or coexisting HS infection is detected. In this case report we present erythema multiforme triggered by HHV-1 infection, and the disease was controlled with continuous oral acyclovir therapy to prevent recurrences.

REFERENCES